REMARKS

Status of the Claims

Claims 12-39 are pending in the application. Claims 12, 16, 17, 21, 22, 26, 27, and 31 have been amended and claims 32-39 have been added. Support for the amendments and new claims can be found in the specification at, e.g., page 13, lines 9-12; page 31, lines 17-22; page 31, line 23 to page 32, line 2; page 31, lines 17-22; and page 21, lines 2-11. No new matter has been added.

35 U.S.C. § 103(a) (Obviousness)

(1) At page 2 of the Office Action, claims 12-21 were rejected as allegedly unpatentable over Carlson et al. (U.S. Patent No. 5,538,852). Applicants respectfully traverse this rejection.

According to the Office Action,

> Carlson et al. do not disclose using competitor as a control in the immunoassay method but the use of a control (standard) to obtain a calibration curve is a well known requirement for the performance of an immunoassay and therefore the use of such calibration curve by Carlson is implied. Since the competitor and analyte antigens bind similarly to the antibody, it would be presumed that either the analyte antigen or the competitor antigen could function equivalently as a control standard.

Applicants traverse the rejection and respectfully submit that it would not have been obvious to the skilled artisan to use a compound of formula (1) as a standard for a calibration curve in a dioxin immunoassay.

According to the claimed immunoassay methods, a compound of formula (1), which is different from the target dioxins, is used as a competitor antigen and <u>as a control standard to obtain a calibration curve</u>.

Carlson et al. disclose immunoassay methods for the detection of polychlorinated biphenyls (PCBs), one type of a dioxin. Carlson et al. describe that certain chlorinated phenoxy conjugate compounds can be used as competitor antigens in the immunoassay. However,

nowhere does Carlson et al. describe a control standard let alone the use of a compound of formula (1) as a control standard in the assay. This is acknowledged by the Office Action, which states that Carlson et al. disclose "competitive immunoassay methods … in which chlorinated phenoxy (Formula I of front page, column 4; compound 15 of Fig. 4 and claim 14) conjugates with BSA or KLH … are used as competitor in the immunoassay method" (page 3, line 17) but "Carlson et al. do not disclose using competitor as a control"(page 3, lines 17-18). However, the Office Action nonetheless asserted that the use of a standard to obtain a calibration curve is implied and "since the competitor and analyte antigens bind similarly to the antibody, it would be presumed that either analyte antigen or the competitor antigen could function equivalently as a control standard" (page 3, lines 20-22). Applicants respectfully disagree.

Since only trace amounts of dioxins are present in environmental samples such as soil and air and in biological samples such as mothers' milk and blood, high precision measurement is paramount to assay dioxins in these samples and obtaining a highly reliable (e.g., accurate, precise and consistent) calibration curve is very important. Moreover, in determining the concentration and Toxicity Equivalent (TEQ) of trace amounts of dioxins, obtaining a reliable calibration curve is also particularly important because the assay results can vary greatly depending on which calibration curve is used as the standard.

When using a compound that is the same as, or similar to, the analyte, a reliable calibration curve is expected because the compound has the same structure and same affinity to an antibody as the analyte has to the antibody. On the other hand, when using a compound that is structurally different from the analyte, a calibration curve that is different from, and thus not necessarily as reliable as, one obtained using the analyte compound would be expected.

Applicants respectfully submit that the compound of formula (1) of the present invention is structurally different from analyte dioxins and as is clear from Carlson et al., when a compound is structurally different from the analyte, the compound has different affinity to an antibody than the analyte has to the antibody.

For example, Carlson et al. disclose using a compound of Formula I or II as a competitor antigen and a compound of Formula III as a hapten (a molecule used as an immunogen to make an antibody) (see column 4 of Carlson et al.). Carlson et al. disclose that <u>to enhance sensitivity of the assay</u>, competitors of Formula I that are structurally less similar to the

hapten compound of Formula III are preferred over competitors of Formula II that are structurally more similar. "Preferably, to improve sensitivity, said competitor will have a lower affinity to said antibodies than said antibodies have to the polychlorinated biphenyls"(column 3, lines 39-41 of Carlson et al.) and "[c]ompetitors of Formula I are preferred as they are expected to provide, in general, greater sensitivity than the biphenyl based competitors of Formula II. Competitors of Formula I are expected to bind anti-hapten antibodies with a lower affinity than the affinity with which PCBs will bind to the anti-hapten antibodies" (column 4, lines 46-51 of Carlson et al.).

Applicants respectfully submit that even if the analyte (i.e., polychlorinated biphenyls) and competitor antigen of Formula I of Carlson et al. bind "similarly" to an antibody, it would not have been obvious to one skilled in the art from Carlson et al. whether a highly reliable calibration curve could be obtained by using as a control standard the competitor antigen in place of the analyte dioxins -- because the competitor antigen and analyte dioxins have different structures and affinities to the antibody.

Therefore, since the compound of formula (1) of the claimed methods is structurally different from the analyte dioxins, it would not have been obvious to the skilled artisan whether a highly reliable calibration curve could be obtained by using as a control standard the compound of formula (1) in place of the analyte. Moreover, it would not have been obvious from Carlson et al. whether the compound of formula (1) of the claimed methods is effective as a control standard for <u>all types of dioxins</u>, i.e., not only for polychlorinated biphenyls described in Carlson et al. but also for polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and coplanar polychlorinated biphenyls (Co-PCBs).

In view of these considerations, applicants respectfully request that the Examiner withdraw the rejection.

(2) At page 4 of the Office Action, claims 22-31 were rejected as allegedly unpatentable over Carlson et al. in further view of Sugawara et al. ((1998) Anal. Chem. 70:1092-1099; page 5, line 9, of the specification). Applicants respectfully traverse this rejection.

According to the Office Action,

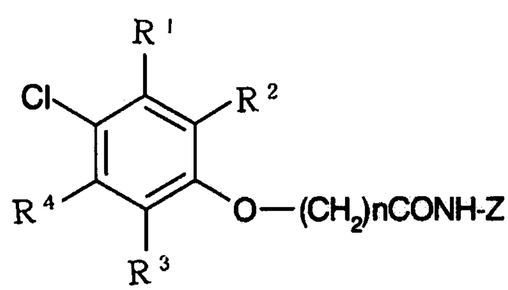
> [a]dmitted prior art disclose that calculation of TEQ value in immunoassay detection of dioxins is common and know in the art for dioxin determination[.]
>
> ....
>
> Therefore, it would have been prima facie obvious to one of ordinary skill in the art...to include calculation of TEQ value in the method of Carlson et al for determining amount of dioxins in a sample.

Applicants respectfully traverse the rejection.

Independent claims 22 and 27 are drawn to immunoassay methods including the steps of: 1) allowing target dioxins in the sample and a competitive antigen to competitively react with a primary anti-dioxin antibody capable of binding to the target dioxins, and determining the amount of competitive antigen-antibody complex from a label incorporated into a secondary antibody binding to the primary antibody;

2) allowing the competitive antigen and

a compound of formula (1) of known concentration



(1)

wherein R^1, R^2, R^3 and R^4 may be the same or different and each represents chlorine or hydrogen, n is an integer from 1 to 10, and represents 1 to 100 amino acid residues to competitively react with the primary anti-dioxin antibody, and determining the amount of competitive antigen-antibody complex from a label incorporated into a secondary antibody binding to the primary antibody;

3) preparing a calibration curve using the amount of competitive antigen-antibody complex determined in step 2);

4) comparing the amount of competitive antigen-antibody complex determined in step 1) with the calibration curve prepared in step 3); and

5) calculating the TEQ of dioxins in a sample.

The Toxicity Equivalent or TEQ, calculated in step 5, is calculated, in part, from the calibration curve (step 3) in the immunoassay using the compound of formula (1). For the reasons set forth above in response to the first obviousness rejection, applicants submit that the use of the compound of formula (1) as a standard and/or in a calibration curve in an immunoassay for dioxin detection is not rendered obvious in view of Carlson et al. Therefore, a subsequent TEQ calculation based on that standard/calibration curve would not have been obvious to the skilled artisan.

In view of these considerations, applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

Applicants submit that all grounds for rejection have been overcome and that all claims are in condition for allowance, which action is requested.

The fee in the amount of $400 for extra claims is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any additional charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 18900-002US1.

Respectfully submitted,

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